Section: Nephrology

Original Research Article

EFFECT OF N-ACETYL CYSTINEON ENDOTHELIAL DYSFUNCTION, BIOMARKERS OF OXIDATIVE STRESS AND INFLAMMATION IN SUBJECTS UNDERGOING HIGH AND LOW FLUX HEMODIALYSIS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Patients with chronic kidney disease are at high risk for cardiovascular morbidity due to CKD induced oxidative stress, inflammation and endothelial dysfunction. N-acetyl cysteine supplementation can replenish the anti-oxidants deficit and thus reduce the risk of cardiovascular morbidity in CKD patients.

Materials and Methods: 40 patients on maintenance hemodialysis were included in this randomized double blind placebo controlled study and were then divided randomly into 4 groups of 10 members each. 600mg of N-acetyl cysteine (twice daily) was given to group 2 (low flux HD) and group 4 (high flux HD), while placebo was given to group 1 (low flux HD) and group 3 (high flux HD). Biomarkers of oxidative stress (Malondialdehyde (MDA), Nitric oxide (NO) and glutathione), inflammation (highly sensitive C-reactive protein (hs-CRP) and endothelial dysfunction (Augmentation pressures and index) were evaluated at 0, 4 and 12 weeks.

Results: The differences in baseline demographic characteristics of all groups were not significant. Patients on high flux hemodialysis (groups 3 and 4) and low flux hemodialysis with NAC (group 2) showed significant reduction in serum MDA and hs-CRP levels, along with significant improvement in serum levels of nitric oxide and glutathione. Group 4 (high flux HD on NAC) showed the most significant changes while group 1 (low flux HD on placebo showed no significant change in any parameters.

Conclusion: Patients on high flux hemodialysis show a significant difference in biomarkers of oxidative stress, inflammation and endothelial dysfunction when compared to patient son low flux hemodialysis. These changes are augmented by usage of N-acetyl cysteine.

Keywords: N-acetyl cysteine, Hemodialysis, high flux and low flux dialyzer, oxidative stress, Malondialdehyde (MDA), C-reactive protein.

INTRODUCTION

Chronic kidney disease (CKD) represents a significant public health challenge, with over 2 million individuals worldwide being diagnosed with CKD, and a substantial proportion of them undergo hemodialysis (HD) or other forms of renal replacement therapy.[1] Diabetes Mellitus, hypertension and dyslipidemia are some of the well-established risk factors which have strong association with cardiovascular morbidity, the leading cause of mortality in patients with chronic kidney disease.[2,3] Imbalance between pro-oxidants (such as increased levels of Malondialdehyde (MDA)) and anti-oxidants

(such as reduced levels of Glutathione) give rise to oxidative stress, which in combination with CKD induced chronic inflammatory state and accumulation of uremic toxins, lead to endothelial dysfunction and increased cardiovascular morbidity in CKD patients.[4,5]

High flux dialysis membranes owing to their greater permeability are capable of clearing middle molecular weight uremic toxins in comparison to low-flux membranes, resulting in decreasing oxidative stress and inflammation. However, hemodialysis itself can induce oxidative stress due to loss of anti-oxidants during the process of dialysis, activation of immune cells and interactions between blood and dialysis membrane.[6,7]

Studies have observed that anti-oxidant therapy is said to ameliorate oxidative stress in CKD patients and therefore mitigate CVD risk. N-acetyl cysteine, a thiol-containing compound, known to replenish endogenous anti-oxidant, glutathione, has shown promising results in reducing oxidative stress induced cardiovascular morbidity in CKD patients.

This studywas done to evaluate the impact of N-acetyl cysteine (600mg twice daily dose) on endothelial dysfunction, oxidative stress, inflammation biomarkers and tolerance in patients undergoing hemodialysis (high-flux and low-flux).

MATERIALS AND METHODS

This prospective randomized double blind placebo controlled study was conducted at the Department of Clinical Pharmacology and Therapeutics in collaboration with the Department of Nephrology, Nizam's Institute of Medical Sciences, Hyderabad, over 12 months duration (May 2018 to April 2019). Ethical Committee approval was taken from the Institutional Ethics Committee (Reference no: EC/NIMS/2155/2018 30th ESGS No.673/2018) and was also registered in Clinical Trial Registry of India (CTRI) (Registration no. CTRI/2018/03/012586). A written informed consent was taken from all the participants prior to the study.

All CKD patients between 18-60 years who were undergoing hemodialysis in the Department of Nephrology, 2 or 3 times a week for a duration more than 3 months up to 2 years; who were naïve to NAC; who were on stable treatment for diabetes and hypertension for the past 8 weeks and who gave their consent to participate in the study were included.

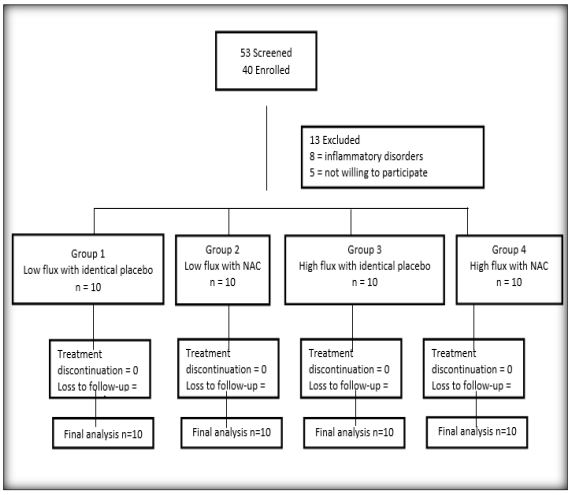
Patients who were on Vitamin C or E or other anti-oxidant supplements for the past 1 month or those with chronic inflammatory diseases; or were alcoholic; or had malignancy; or with pre-existing haematological disorders; or with hypersensitivity to NAC; or were enrolled in other drug trials were excluded. Pregnant women, lactating mothers and post renal transplantation patients were also excluded from the study. All study subjects were screened by medical history, clinical examination and necessary laboratory investigations

A total of 53 Hemodialysis patients were screened with baseline investigations and were assessed for their eligibility in the study. A total of 40 patients were selected to be included in the study based on their baseline parameters and willingness to enroll into the study. By means of random allocation, these 40 participants were divided into four groups in the ratio of 1:1:1:1 by means of random allocation. Allocation concealment was done using sealed envelopes by a third person. Groups 1 and 2 consisted of patients on low-flux hemodialysis, while groups 3 and 4 consisted of patients on high-flux hemodialysis. Study participants belonging to Groups 2 and 4 were given 600mg of N-acetyl cysteine twice daily for 12 weeks, while those of Groups 1 and 3 were given NAC identical placebo twice daily for 12 weeks (NAC identical placebo contained the following inactive ingredients - 49.7% of microcrystalline cellulose, 49.5% of lactose and 0.8% of magnesium stearate). The study medications were provided to the patients by the investigator. Compliance was assessed by pill count method.

Blood samples were collected at the baseline (0 week), 4 weeks, and at the end of 12 weeks treatment to estimate biomarkers of oxidative stress and inflammation - glutathione, serum malondialdehyde (MDA), Nitric oxide (NO) and high-sensitivity C-reactive protein (hs-CRP) levels, laboratory parameters for safety which included complete blood picture, liver function and renal function tests. Endothelial function was evaluated using pulse wave analysis by measuring augmentation index (Aix), augmentation pressure(AP) at baseline, at 4 weeks and 12 weeks.

Primary endpoints for the study included changes in biomarkers of oxidative stress (serum MDA, GSH and NO); changes in endothelial function (augmentation pressure (AP) and index (Aix)). The secondary endpoint included tolerability to the study medication. Study participants were allowed to withdraw at any time during the study in the light of occurrence of adverse events or due to non-compliance to the prescribed drug regimen.

Statistical analysis was performed using the Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Data was presented as mean ± SD. Comparisons between groups was assessed by ANOVA followed by post hoc analysis. Comparison between pre and post treatment within group calculated by repeated measures ANOVA test. P value <0.05 was considered as Level of significance.



RESULTS

A total of 53 patients were screened out of which 13 patients were excluded (8 due to inflammatory disorders and 5 due to unwillingness to participate). 40 patients were included in the study, who were divided into 4 groups randomly. Table 1 shows the baseline demographic characteristics in all groups. Male predominance was observed in all 4 groups. There was no significant difference in the age, BMI and gender distribution between the group, which is suggestive of uniformity in study sample.

Table 2 shows the changes in biomarkers of oxidative stress (MDA, NO, glutathione andHighly sensitive CRP) and endothelial dysfunction (Augmentation pressures and augmentation index) at baseline, 4 weeks and 12 weeks of all 4 groups.

Malonialdehyde (MDA), a biomarker of oxidative stress was significantly reduced from baseline to 12 weeks in groups 2,3 and 4 (p = <0.001), with the highest reduction observed in group 4 (-1.32 µM/L, 24.37%; p = <0.001). There was no change in MDA levels in Group 1 ( ) Intra-group comparison revealed significantly reduced MDA levels in high flux HD on NAC group than any other groups.

Nitric oxide levels which represent the vascular function, was significantly improved in groups 2, 3 and 4. There was no significant change in levels of NO in group 1 ( ). At end of 12weeks, groups 2, 3 and 4 had shown significant improvement in NO levels with group $ showing the highest increase (+16.12 µM/L, 45.38%, p < 0.001).

Serum glutathione levels have shown a significant rise in groups 2, 3 and 4. However, group 1 shows non-significant change in serum glutathione levels (-0.42 µM/L, -0.11%, p value = not significant). By end of 12 weeks, groups 2 – 4 have shown a significant improvement in glutathione levels, with the maximum rise in group 4 (+83.98 µM/L, 23.99% by 12 weeks, p < 0.001).

Highly sensitive C-reactive protein levels have shown a significant reduction in groups 2-4, with the maximum change in group 4 (-1.97 mg/L, -45.28%' p = <0.001). Group 1 exhibited no change by 12 weeks (0.18 mg/L, 4.26%, p = 1.00).

Augmentation pressure, a marker of endothelial dysfunction was significantly reduced in groups 2 and 4 by 4 weeks (p value = 0.03 and < 0.001, respectively for groups 2 and 4). This reduction was greater by the end of 12 weeks (p value = 0.001 and <0.001, respectively). Group 1 observed no change in augmentation pressure by end of 12 weeks. The greatest reduction of AP was seen in group 3 (-6.6 mmHg, -36.6%, p value = <0.001).

Another marker of endothelial dysfunction, augmentation index (Aix), was also significant reduced in groups 2,3 and 4, with the highest reduction with group 4 by end of 12 weeks (-7.0, -21.94%, p value = <0.001). Group 1 has shown no change. However, intragroup comparison shows that there was no statistically significant change in mean augmentation index seen at 4,12 weeks between all the 4 groups.

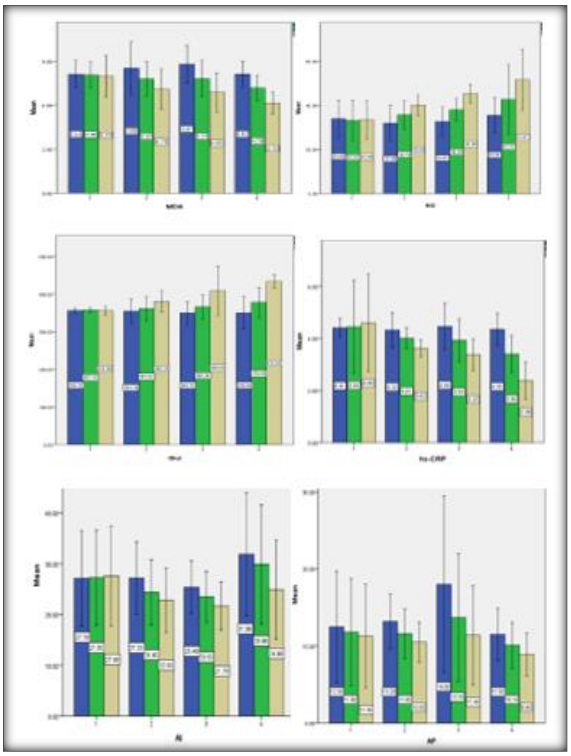


Figure 1: Figure 1-6: Bar charts depicting changes in various parameters at baseline (blue bars), 4 weeks (green bars) and 12 weeks (cream coloured bars). MDA – Malondialdehyde; NO – nitric oxide; Glut – Glutathione; hs-CRP – Highly sensitive CRP; AI – Augmentation index; AP – Augmentation pressure

Table 1: Baseline demographic characteristics

Characteristic	Group 1 (n=10) Low flux with placebo	Group 2 (n=10) Low flux with NAC	Group 3 (n=10) High flux with placebo	Group 4 (n=10) High flux with NAC	P value
Gender (M/F)	7M/3F	6M/4F	7M/3F	6M/4F	0.932

Age (years)	42.00±13.09	45.90±10.32	46.30±11.51	38.70±10.49	0.410
BMI (kg/m^2)	22.65±4.25	24.47±3.42	22.07±4.03	23.98±3.03	0.448

Table 2: Comparison of changes in oxidative and endothelial dysfunction markers in groups

Parameter		Group 1 Low flux with placebo	Group 2 Low flux with NAC	Group 3 High flux with placebo	Group 4 High flux with NAC
Malondialdehyde (MDA in µM/L)	Baseline	5.41±0.31	5.69±0.59	5.87±0.43	5.42±0.29
	4weeks	5.37±0.29	5.20±0.38	5.20±0.41	4.78±0.28
	12 weeks	5.32±0.47	4.73±0.45	4.59±0.44	4.09±0.25
	P value	4 weeks = 0.776 12 weeks = 1.0	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = <0.0001 12 weeks = <0.0001
NO (µM/L)	Baseline	33.98±4.24	31.95±4.08	32.64±3.29	35.53±4.06
	4 weeks	33.21±4.57	35.78±3.18	38.03±2.60	42.72±7.94
	12 weeks	33.49±4.31	40.04±2.46	45.29±2.11	51.66±6.87
	P value	4 weeks = 0.428 12 weeks = 1.0	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = 0.03 12 weeks = <0.0001
Glutathione (µM/L)	Baseline	356.31±3.06	354.73±16.31	349.75±15.21	349.96±21.71
	4 weeks	357.17±3.37	361.01±16.10	366.34±15.82	378.06±19.83
	12 weeks	355.89±5.48	380.27±14.04	408.60±32.96	433.94±8.78
	P value	4 weeks = not significant 12 weeks = <0.001	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = 0.03 12 weeks = <0.0001
Highly sensitive C-reactive Protein (mg/L)	Baseline	4.41±0.17	4.32±0.33	4.45±0.44	4.35±0.31
	4 weeks	4.44±0.89	4.01±0.20	3.93±0.40	3.40±0.35
	12 weeks	4.59±0.93	3.62±0.16	3.37±0.30	2.38±0.35
	P value	4 weeks = 1.00 12 weeks = 1.000	4 weeks = 0.012 12 weeks = <0.0001	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = <0.001 12 weeks = <0.0001
Augmentation pressure (mm Hg)	Baseline	12.50±7.23	13.20±3.52	18.0 ±11.47	11.50±3.40
	4 weeks	12.10±7.09	11.6 ±3.20	13.70±8.31	10.10±2.96
	12 weeks	12.0±6.34	10.50±2.59	11.40±6.43	8.90±2.76
	P value	4 weeks = 0.110 12 weeks = 0.638	4 weeks = 0.03 12 weeks = 0.001	4 weeks = 0.552 12 weeks = 0.145	4 weeks = <0.001 12 weeks = <0.0001
Augmentation Index	Baseline	27.10±9.38	27.20±7.13	25.40±5.16	31.90±12.13
	4 weeks	27.30±9.35	24.40±6.44	23.50±5.01	29.90±11.74
	12 weeks	27.60±9.81	22.80±6.33	21.70±4.76	24.90±9.75
	P value	4 weeks = 1.00 12 weeks = 1.000	4 weeks = 0.012 12 weeks = <0.0001	4 weeks = <0.0001 12 weeks = <0.0001	4 weeks = <0.001 12 weeks = <0.0001

Overall, 4 adverse events were noted in 40 enrolled patients. Group 2 had the most adverse effects of all. The most common adverse events reported were gastrointestinal symptoms.

Table 3: Adverse effects

Adverse effects	Group1 (Low flux with placebo) n=10	Group2 Low flux with NAC) n=10	Group3(High flux with placebo) n=10	Group4(High flux with NAC) n=10
Gastrointestinal discomfort	0	1	0	1
Nausea	0	1	0	0
Giddiness	0	0	0	1

DISCUSSION

Exogenous anti-oxidants such as N-acetyl cysteine are said to reduce the oxidative stress generated in CKD patients on hemodialysis. This randomized controlled trial was done to evaluate the efficacy of N-acetyl cysteine versus placebo on reducing oxidative stress in patients undergoing low flux versus high glux hemodialysis. 40 patients were divided in 4 groups of 10 members each. Patients on low flux hemodialysis were in group 1 and 2 who received placebo and NAC, respectively, while patients on high – flux hemodialysis were in groups 3 and 4 who received placebo and NAC respectively. Effects of NAC on oxidative stress: Malondialdehyde, one of the biomarker of oxidative stress was found to be significantly reduced in patients of high flux group (group 3 and 4) and low flux group receiving NAC (group 2). There was no change in low flux group on placebo. High flux HD

patients receiving NAC showed the highest reduction of MDA levels, thereby suggesting a positive role of NAC. Studies done by Trimachi et al,[8] and Giannikouris et al,[9] also resonate similar findings.

While both the high flux groups (groups 3 and 4) and low flux group on NAC showed increased nitric oxide (NO) levels, low flux group on placebo had no change in present study. Hemodialysis patients exhibit high levels of Asymmetric dimethyl arginine (ADMA), a molecule with inhibitory action on nitric acid synthetase (NOS) and low levels of the endothelium-derived relaxant factor NO.[10] Giannikouris et al,[9] suggest a beneficial effect on the levels of NO and ADMA, which could be attributed to the restoration of redox balance as a result of oxidative stress reduction.

In present study, it was observed that high flux groups (groups 3 and 4) and low flux group on NAC have shown significant improvement in glutathione values at 4, and 12 weeks of treatment compared to baseline. Group 1 (Low flux without NAC) has not shown any significant change from baseline. Khazim et al,[11] conducted a cross-sectional study in 33 maintenance HD patients and 21 healthy controls and found that compared to controls, the RBC GSH/GSSG redox potential was significantly lower and both glutathionylated and cysteinylatedhemoglobins were significantly higher in HD subjects. Ideally, the reduced stores of glutathione can be replenished by NAC administration as exogenous glutathione administration has poor bioavailability and is unable to cross phospholipid bilayer.[12,13] Gibson et al.[14] demonstrated that NAC increased intraplatelet levels of GSH, decreased ROS detection and reduced platelet activation in vitro.

Effect of NAC on inflammation: CRP, a large, non-dialyzable acute phase reactant, rises rapidly and has a short life, making it ideal for identifying acute inflammation.[15-17] In present study, highly sensitive C-reactive protein (hs-CRP) was significantly reduced in high flux groups (group 3 and 4) and low flux group on NAC (group 2). Group 1 had no significant change. Saddadi et al,[18] gave 600mg of NAC to 24 CKD patients on HD and observed a significant decrease in levels of hs-CRP and IL-6. Purwanto and Prasetyo et al,[19] concluded that compared to placebo, NAC administration significantly reduced the levels of several inflammatory biomarkers such as IL-1, IL-6, hs-CRP, TNF, and procalcitonin. Hadim et al,[20] also had similar findings in their study.

Effect of NAC on endothelial dysfunction: In patients with CKD, Multiple intrinsic and extrinsic factors interplay to induce endothelial dysfunction and atherosclerosis.[21,22] In present study, patients who received NAC (groups 2 and 4) had significant reduction in augmentation pressure when compared to those who received placebo (groups 1 and 3).The results of this study were similar to the study by Wittstock et al,[23] Sahin et al,[24] and Tepel et al.[25]

Tolerability: The patients in this study tolerated NAC well with minimal adverse events. A total of 4 adverse events were noted in a total of 40 enrolled patients. However, according to previosu studies, adverse effects with NAC depend on the route of administration. Mild reactions – such as nausea, vomiting and cutaneous reactions (pruritus and erythema) – are common with the IV preparation. Although severe systemic reactions are uncommon, incidents of anaphylactoid reactions with intravenous route have been reported.[26-28]

CONCLUSION

Shifting HD settings from low flux to high flux dialyzer along with supplementation of N-acetyl cysteine (oral or intravenous administration) showed significant beneficial effects in reducing oxidative stress, inflammation and endothelial dysfunction than single intervention. However, further studies in large cohorts of dialysis patients are required, to establish causality between antioxidant supplementation with N-acetylcysteine, changing the flux of membranes on the clinical end-points of cardiovascular diseases and all-cause mortality.

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Conflicts of interest: The authors have no conflicts of interest to declare.

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